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Oocyte-somatic cell communication and microRNA function in the ovary:

Communication ovocyte-cellule somatique et fonction des microRNA dans l'ovaire

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Abstract

An enormous amount of knowledge about the ovary has been generated over the last two decades, due in part to the development of strategies to genetically manipulate the mouse using embryonic stem cell technology. Our group and others have identified multiple factors that are important and essential at all stages of ovarian folliculogenesis from formation of the primordial factor to ovulation. It is obvious that an oocyte, the key cargo of the ovary, and the surrounding granulosa cells, the support cells of the follicle, entertain a dialog that is key for granulosa growth and differentiation and oocyte growth, maturation, and fertilization. In addition to the involvement of genes in these processes, small non-coding RNAs including microRNAs and siRNAs have been implicated as key regulators, especially in the oocyte. These studies have direct implications for human fertility control in the assisted reproductive technology (ART) laboratory.

Keywords

MicroRNAs; siRNAs; Ovarian folliculogenesis

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Conflict of interest statement
None.

1. Introduction

The first knockouts of genes in mice were achieved in the late 1980s. However, the last two decades have seen the publication of a wealth of information on the development and physiology of the mammals using the newfound technology. Included among this list are over 500 mutant mouse models that have a fertility phenotype [1,2]. In particular, our group has been focused on understanding the factors involved in intercellular communication between the oocyte and the surrounding cumulus cells in the periovulatory follicle [3]. In addition, not only are genes encoding proteins involved in this process but also small non-coding RNAs that function to regulate gene expression [4].

2. Oocyte-somatic cell communication

Beginning with formation of the primordial follicle, the oocyte and its surrounding granulosa cells communicate, a dialog that is essential for fertility. Although all of the secreted factors required in primordial follicle recruitment have not been identified, it is obvious that the oocyte plays a key role at later stages. At the transition from the primary (one layer) follicle to the secondary (two or more layers preantral) follicle, growth differentiation factor 9 (GDF9) in mouse [5] and bone morphogenetic protein 15 (BMP15) in sheep [6] are essential and critical for fertility. GDF9 and BMP15, members of the transforming growth factor β (TGFβ) superfamily that play key roles in mammals [7], are most closely homologous to each other in the family and are synthesized in oocytes beginning at primordial follicle recruitment [8–10].

The transition from preantral to antral follicles requires extragonadal signaling. The pituitary glycoprotein hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) have distinct roles in the regulation of folliculogenesis [4]. In the absence of FSH the ovarian follicle halts at the large preantral follicle stage [11,12]. However, in the presence of FSH, many of the intercellular connections between the granulosa cells and the oocyte are disrupted, allowing an antrum to form [13], the first step in the formation of a preovulatory follicle. The preovulatory follicle separates the granulosa cell component into two parts: those lining the wall and adjacent to the basement membrane are called the mural granulosa cells whereas those adjacent to the oocyte are called the cumulus granulosa cells. LH plays a dual role in the follicle, stimulating androgen synthesis by the thecal cells and inducing ovulation of a cumulus cell-oocyte complex (COC) [4,14–16].

In addition to a role of LH in ovulation, LH works indirectly with the oocyte to induce the process of cumulus expansion, the laying down of a proteinaceous and hyaluronic acid rich matrix [1,2,4]. Multiple genes have been shown to play roles in cumulus expansion (Table 1). Oocyte secreted factors including GDF9, BMP15, and fibroblast growth factor 8 (FGF8) are required for this process, and the Eppig laboratory has elegantly demonstrated important roles of the oocyte in regulation of cumulus cell amino acid transport, glycolysis, and cholesterol biosynthesis [17–20]. Because LH receptors are not present on cumulus cells, LH acts by inducing the secretion of epidermal growth factor (EGF)-like ligands from the mural granulosa cells and subsequent synergism with the oocyte-secreted proteins to regulate cumulus cell functions [21]. These signaling pathways are important for the ART laboratory.

3. Specific small RNAs in the ovary

MicroRNAs are small RNA molecules that are approximately 22 nucleotides in length [40]. These molecules are thought to function as repressors of gene expression by blocking mRNA translation and/or destabilizing and degrading the mRNA transcript [41]. Using mouse modeling techniques, microRNAs have been implicated to play roles in ovarian

function and development. Although microRNAs and/or small interfering RNAs (siRNAs) are required in the oocyte (see next section), microRNAs likely function only through “fine tuning” of gene expression in granulosa cells. To date, most of the data involves microRNA profiling of ovarian tissues, and therefore there is only speculation of the actual function of specific microRNAs (Fig. 1) [42,43].

Nobox, newborn ovary homeobox-encoding gene, is a homeobox gene critical for oocyte development. *Nobox* null mice are infertile due to early ovarian insufficiency, demonstrating a block from the primordial to primary follicle stage [44,45]. Characterization of the microRNA profiles in wild type newborn ovaries revealed especially high levels of miR-709 [46], an abundant microRNA in mouse embryos [47]. Additionally let-7 microRNA family members were abundant as well in newborn ovaries. Differentially expressed microRNAs between the *Nobox* null and wild type mouse newborn ovaries included only modest fold changes in microRNA levels [46]. However, the functional significance of these microRNAs in the *Nobox* null ovaries is not known (i.e., it is not clear whether the microRNA changes are a consequence of major changes in downstream targets of Nobox, whether they are directly regulated by Nobox, and/or if the microRNA changes play any major roles in the primordial follicle).

Lhx8 is a Lim homeodomain protein important for ovarian development [48]. Similar to Nobox, Lhx8 is required for transition from the primordial to primary follicle stage and is required for fertility. *In silico* targeting algorithms speculate that miR-93 may target this important gene in ovarian development [49], although functional relevance of miR-93 in reproduction will have to await conditional knockout of miR-93 in oocytes.

MicroRNAs in granulosa cells are hormonally regulated. Using mouse mural granulosa cells treated with human chorionic gonadotropin (hCG), a set of hormonally responsive microRNAs was described [50]. In particular, miR-132 and miR-212 were significantly upregulated by hCG. *In silico* targeting speculated 77 common targets between these two microRNAs and hCG responsive genes. Specific targeting results suggest that miR-132 and miR-212 inhibit C-terminal binding protein 1 (Ctbp1) protein synthesis. However, the role of CTBP1 in ovarian function is not known.

Lastly, specific microRNA expression on steroid hormone expression from human primary granulosa cells has been described. Multiple microRNAs affected production of progesterone, testosterone, and estradiol from these primary cell cultures [51]. However, they only examined 187 individual microRNAs out of the now 750 known human microRNAs, based on miRBase version 14.0, release September 2009. Therefore, the global effect of microRNAs on ovarian function is still undiscovered.

3.1. Global disruption of small RNA synthesis in various compartments of the ovary

Dicer1 is an endoribonuclease III essential for microRNA synthesis. It is responsible for cleavage of the precursor microRNA species with its stem-loop structure to the double stranded mature microRNA and corresponding star form [52]. *Dicer1* is essential for mammalian development as deletion of Dicer1 through traditional knockout mouse technology has shown embryonic lethality at day e11.5 [53].

Mutant mice with a *Dicer1* hypomorphic allele ($Dicer1^{d/d}$) are infertile [54]. However, these mice were unable to maintain a pregnancy, presumably due to impaired corpus luteum function. Additionally, the corpora lutea of these mice had abnormal angiogenesis, likely through dysregulation of the antiangiogenic factor, tissue inhibitor of metalloproteinase 1 (Timp1). *In silico* microRNA targeting algorithms predict that miR-17-5p and let-7b target Timp1. Both of these microRNAs were present in wild type ovaries but not in the *Dicer1*

hypomorphic ovaries. Additional functional studies validated the role of miR-17-5p and let-7b on Timp1 activity and angiogenic function. Thus, miR-17-5p and let-7b play a role in angiogenesis in the mouse corpus luteum.

Dicer1 is highly expressed in the mouse oocyte and is regulated with folliculogenesis and embryogenesis [55]. Conditional deletion of *Dicer1* in the oocyte using a cre recombinase driven by the zona pellucida protein 3 (*Zp3*) promoter, which drives cre expression in the postnatal oocyte, results in infertile mice. Oocyte growth and development and responses to gonadotropins were normal in these mice. However, the oocytes had meiotic defects due to defective spindle formation. MicroRNA profiling suggest that miR-103, miR-16, miR-30b, miR-30c, and let-7d target genes important in spindle organization. However, these defects in spindle formation may also be attributed to disruption of siRNAs as Dicer1 is also important for siRNA processing. Additionally, *Dicer1* knockout oocytes have increased expression of mRNA targets of endogenous siRNAs [56,57]. Since these endogenous siRNAs appear to play a significant role in oocytes, the relative significance of microRNAs versus siRNAs in oocytes is unknown.

Dicer1 is expressed in the somatic cells of the ovary but expression does not vary with folliculogenesis. However, conditional deletion of *Dicer1* in the somatic cells of the female reproductive tract using *Amhr2-cre* leads to infertility in female mice due mainly to the formation of oviductal diverticuli. However, unstimulated ovaries of these mice have normal histology. The presence of the oviductal diverticuli does not allow the fertilized oocytes and embryos to transit to the uterus [58–62].

Recently, the ovaries from the *Amhr2-Dicer1* cKO mice were found to have a significant decrease in miR-503 expression compared to controls [62]. Additionally, this change in expression was dependent on hormonal manipulation. MiR-503 is a target of cyclin D2 (Ccnd2), which is important for proliferation during folliculogenesis. Therefore, miR-503 could play a role in folliculogenesis; however, miR-503 likely plays a minimal role functionally since the oviductal diverticuli of normally cycling Amhr2-Dicer1 cKO mice contain hundreds of oocyte remnants and embryos [58], indicating that global depletion of small RNAs in granulosa cells does not grossly disrupt normal ovarian function.

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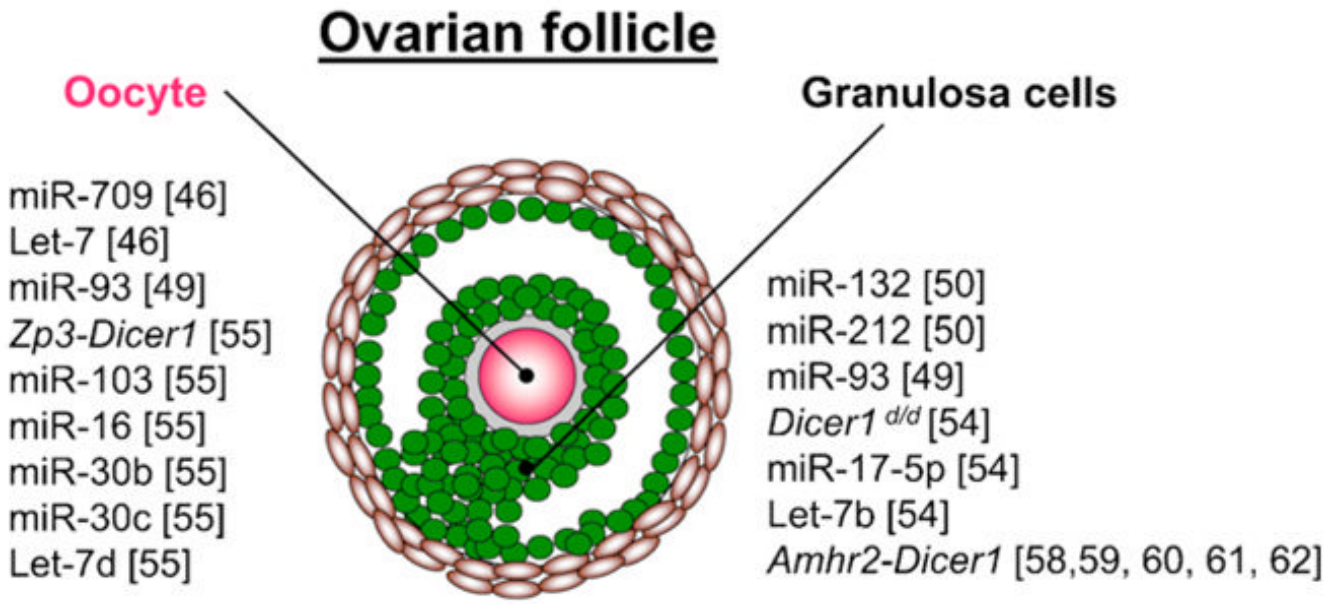

Fig. 1.
MicroRNAs play a functional role in the oocyte and the ovarian follicle. *Les microARN jouent un rôle fonctionnel dans l'ovocyte et le follicule ovarien.*

Table 1

Mouse models with defects in cumulus expansion. For more detailed information, refer to reference [4].

Gene (symbol)	Fertility status	Ref
Prostaglandin-endoperoxide synthase 2 (*Ptgs2*; Cox2)	Mostly infertile	[22,23]
Prostaglandin E receptor 2, subtype EP2 (*Ptger2*)	Subfertile	[24–26]
Pentraxin 3 (*Ptx3*)	Subfertile	[27,28]
Tumor necrosis factor α induced protein 6 (*Tnfaip6*)	Infertile	[29]
Sulfotransferase family 1E, member 1 (*Sult1e1*)	Subfertile	[30,31]
Alpha 1 microglobulin/bikunin (*Ambp*)	Subfertile	[32,33]
Amphiregulin (*Areg*)	Subfertile	[34]
Bone morphogenetic protein 15 (*Bmp15*)	Subfertile	[35]
Bone morphogenetic protein receptor, type IB (*Bmpr1b*)	Subfertile	[36]
Epiregulin ($Ereg^{wa2/wa2}$; hypomorph)	Subfertile	[34]
Mitogen-activated protein kinases 3 and 1 ($Mapk3^{-/-}$ *Mapk1* cKO)	Infertile	[37]
Nuclear receptor subfamily 5, group 2, member 1 (*Nr5a1*; Sf1, steroidogenic factor 1) (cKO)	Infertile	[38]
Nuclear receptor subfamily 5, group 2, member 2 (*Nr5a2*; Lrh1, liver receptor homolog 1) (cKO)	Infertile	[39]

cKO: conditional knockout.